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# An efficient copper-catalyzed synthesis of anilines by employing aqueous ammonia†

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**Under the catalysis of CuI/2-carboxylic acid-quinoline-*N*-oxide, the cross coupling reactions between aryl iodides or bromides and aqueous ammonia proceed very well to afford *N*-unprotected aniline derivatives in excellent yields. This inexpensive catalytic system shows great functional group tolerance and excellent reaction selectivity.**

Aryl amines in general are useful intermediates in pharmaceuticals, agrochemicals, and polymers.[1] The traditional method for the preparation of primary aryl amines is by amination of the corresponding aryl halides using ammonia or ammonium hydroxide as the nucleophile under high temperature and pressure. Recently, the palladium-catalyzed amination of aryl halides with ammonia or ammonia surrogates has been reported.[2,3] However, the drawbacks of these methods are the use of strong bases, a toxic and expensive metal, and sophisticated supporting ligands. Only a few examples of the copper-catalyzed amination of aryl halides with aqueous ammonia under mild conditions have been reported.[4,5] It is highly desirable to develop more efficient, versatile, and facile ligands to further improve the efficiency and generality of the copper-catalyzed amination of aryl halides with aqueous ammonia under relatively mild conditions.

More recently, we developed a series of new ligands for the copper-catalyzed C–N coupling reaction under relatively mild conditions (Fig. 1).[6,7] In this paper, we report an efficient amination of both aryl iodides and bromides under very mild conditions by using aqueous ammonia in a catalytic system, which uses a less toxic and inexpensive metal, of 20% CuI and 40% 2-carboxylic acid-quinoline-*N*-oxide ligand.

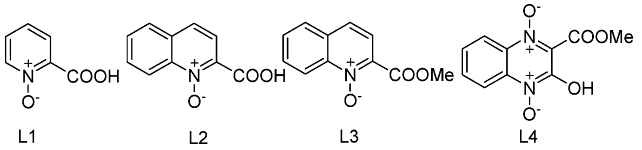
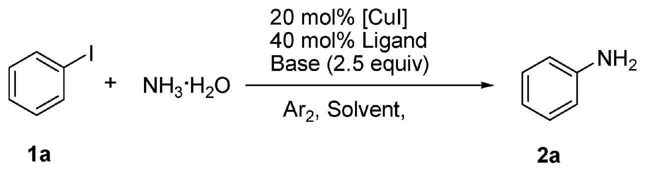


**Fig. 1** Structure of designed ligands.

**Table 1** Amination of iodobenzene under different conditions[a]



| Entry | Ligand | Base | Copper source | Solvent | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | L1 | $K_2CO_3$ | CuI | DMSO | 52 |
| 2 | L2 | $K_2CO_3$ | CuI | DMSO | 93 |
| 3 | L3 | $K_2CO_3$ | CuI | DMSO | 84 |
| 4 | L4 | $K_2CO_3$ | CuI | DMSO | 87 |
| 6 | L2 | $K_2CO_3$ | CuI | DMF | 57 |
| 7 | L2 | $K_2CO_3$ | CuI | toluene | 13 |
| 8 | L2 | $K_3PO_4$ | CuI | DMSO | Trace |
| 9 | L2 | $Cs_2CO_3$ | CuI | DMSO | 90% |

[a] **1a** (1.0 mmol), commercial 28% aqueous $NH_3$ (5 equiv), 20 mol% CuI, 40 mol% ligand, base (2.0 mmol), solvent (2 mL), Ar, 50 °C, 12 h. [b] Isolated yield.

We initially chose the coupling of iodobenzene and aqueous ammonia as the model reaction for optimization of the reaction conditions. We were pleased to find that, with DMSO as the solvent, this reaction proceeded at 50 °C to give aniline in 52% yield in the presence of catalytic amounts of CuI and the ligand picolinic acid-*N*-oxide (**L1**) (Table 1, entry 1). The catalytic activity of the other ligands (L2–L4) was also evaluated in the same reaction system, and L2 gave the highest yield (93%, entry 2). This might be due to the fact that there is a compromise between the solubility of the ligand in the water phase and its chelating with the copper ion ability, which may explain the similar yields observed in the presence of **L2** and **L4** (the former is more soluble in water but less electron-donating than the latter). Other solvents such as DMF and toluene were investigated, using CuI as the catalyst and **L2** as the ligand, and the results showed that DMSO was the best solvent (entries 2, 6, 7). Several bases were screened using the same model substrate and supporting ligand **L2**. $K_2CO_3$ was most effective in DMSO solvent (entries 2, 8, 9). By a systematic variation of the reaction parameters, the optimal condition was the 20 mol% CuI as the catalyst, 40 mol% **L2** as the ligand, DMSO as the solvent, and $K_2CO_3$ as the base at 50 °C.

The optimized reaction conditions were then explored by varying aryl iodides and the results are summarized in Table 2. In general, the coupling reactions were performed well for most

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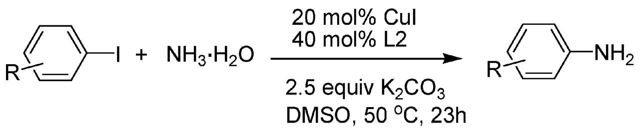
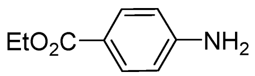
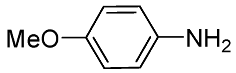
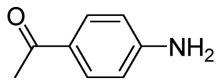
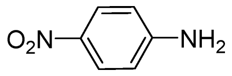
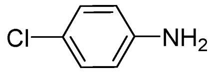
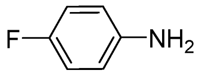
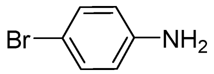
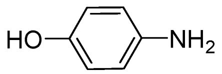
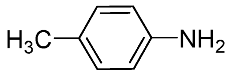
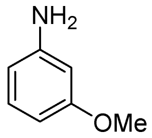
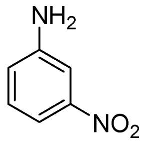
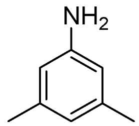
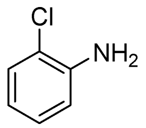
† Electronic supplementary information (ESI) available: Detailed experimental section and NMR spectra. See DOI: 10.1039/c1ob06208e

**Table 2** CuI-catalysed amination of aryl iodides[a]



| Entry | Product | Yield[b] (%) |
|---|---|---|
| 1 |  | 91 |
| 2 |  | 90 |
| 3 |  | 94 |
| 4 |  | 89 |
| 5 |  | 92 |
| 6 |  | 91 |
| 7 |  | 83 |
| 8 |  | 90 |
| 9 |  | 94 |
| 10 |  | 90 |
| 11 |  | 92 |
| 12 |  | 92 |
| 13 |  | 87 |

[a] Reaction conditions: ArI (1.0 mmol), 28% aqueous $NH_3$ (5.0 mmol), CuI (0.20 mmol, 20 mol%), and L2 (0.4 mmol, 40 mol%) in 2.0 mL of DMSO at 50 °C. [b] Isolated yield.

of the substrates examined with 83–94% yields. In addition, the reaction showed a great tolerance to a range of functional groups including ester, ketone, nitro, or hydroxy moiety (entries 1–4, 8, 11). Remarkably, sterically hindered aryl iodide also afforded the coupling product in good yield (entry 13). When halide substituted aryl iodides were used, the coupling takes place selectively at an iodo part in the presence of other halide group (entries 5–7).

Because of their low cost and ready availability, aryl bromides are of much greater interest for industrial applications. We further investigated the potential catalytic efficiency of the CuI/L2 system for the coupling between aryl bromides and aqueous ammonia. As shown in Table 3, all the examined aryl bromides coupled with aqueous ammonia with excellent yields at 80 °C. Both electron-rich and electron-deficient aryl bromides, no matter whether at the *para*- or *meta* positions, are suitable substrates for this reaction, and showing similar reactivity. High yields were obtained even for those aryl bromides with an electron-donating group (entries 2–4 and 11–14). We were pleased to find that the reaction of 4-bromotoluene with aqueous ammonia, which had been considered as a difficult case for the copper-catalysed C–N coupling reation,[4a] gave the coupling product at 80 °C in 90% yield (entry 2). We were also successful in applying the procedure to heterocyclic aromatic bromides, which are important pharmaceutical intermediates (entries 14 and 15).

Furthermore, as described in Fig. 2, we have formulated a possible mechanism for the copper-catalyzed amination of aryl halides with aqueous ammonia. We proposed that the chelating CuI with 2-carboxylic acid-quinoline-*N*-oxide (**L2**) formed a six-member reactive species **A**, and the subsequent oxidative addition of the chelating with aryl halides led to the intermediate **B**. In the presence of base, aqueous ammonia with intermediate **B** readily to afford intermediate **C**, followed by reductive elimination to provide the desired product and regenerate active Cu(I) species **A**.

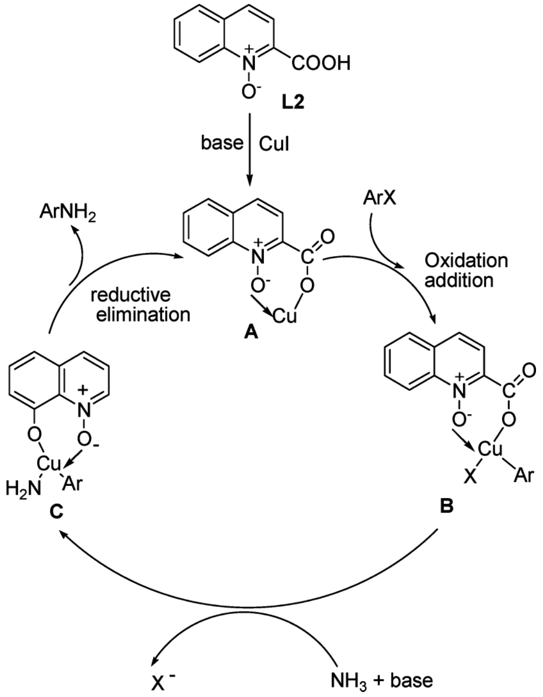
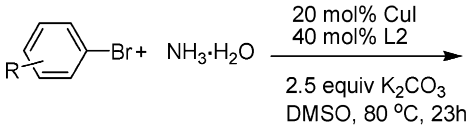


**Fig. 2** Proposed mechanism.

**Table 3** CuI-catalysed amination of aryl bromides[a]



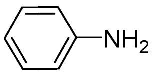
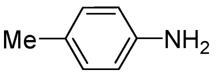
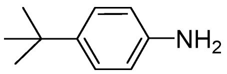
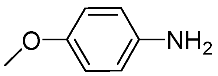
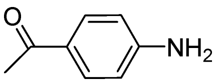
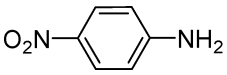
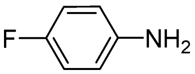
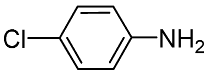
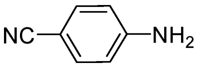
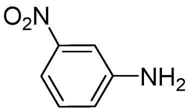
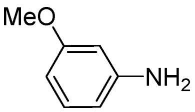
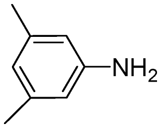
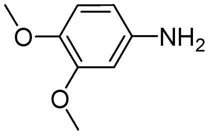
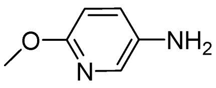
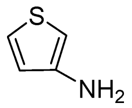
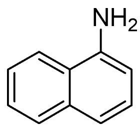
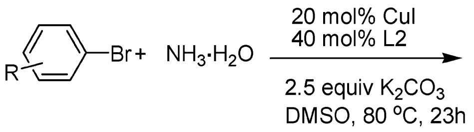
| Entry | Product | Yield[b] (%) |
|---|---|---|
| 1 |  | 98 |
| 2 |  | 90 |
| 3 |  | 82 |
| 4 |  | 97 |
| 5 |  | 93 |
| 6 |  | 96 |
| 7 |  | 93 |
| 8 |  | 88 |
| 9 |  | 93 |
| 10 |  | 95 |
| 11 |  | 93 |
| 12 |  | 91 |
| 13 |  | 96 |
| 14 |  | 95 |
| 15 |  | 86 |
| 16 |  | 92 |

**Table 3** (*Contd.*)



[a] Reaction conditions: ArBr (1.0 mmol), 28% aqueous $NH_3$ (5.0 mmol), CuI (0.20 mmol, 20 mol%), and L2 (0.4 mmol, 40 mol%) in 2.0 mL of DMSO at 80 °C. [b] Isolated yield.

In summary, we have developed an efficient, practical, and economical protocol of Cu-catalyzed coupling of aryl iodides and bromides with aqueous ammonia. A wide range of aryl iodides or bromides bearing both electron-donating and electron-withdrawing substituents were found applicable to this coupling reaction. In addition, our inexpensive catalytic system shows great functional group tolerance. Thus our results may provide a practical new route for the industrial scale synthesis of primary aryl amines.

## Acknowledgements

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